McMaster University

Benzodiazepine-free Cardiac Anesthesia for Reduction of Postoperative Delirium (B-Free): A Cluster-Randomized Crossover Trial

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PACT | Canadian Perioperative Anesthesia Clinical Trials

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Background

- Delirium = acute disorder of cognition
  - >15% of patients **after** cardiac surgery

- Serious problem for patients and systems:
  - prolongs hospital stay
  - cost per patient >$10,229 USD
  - 30% develop PTSD
  - 32% increase in odds of in-hospital mortality

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Background

- Benzodiazepines **before and after** cardiac surgery
  - associated with delirium
  - guidelines recommend avoidance

- Benzodiazepine use **during** cardiac surgery common
  - believed to prevent intraoperative awareness
  - given to 90%

No trial has examined effect of restricting intraoperative benzodiazepines

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Study question

Does institutional policy of benzodiazepine-free cardiac anesthesia reduce incidence of delirium up to 72h after cardiac surgery?

Cluster Crossover trial design

- Selected because:
  - cardiac surgical care provided using standardized care pathways
  - anesthesiologists choose benzodiazepines (or not) based on preference
  - best way to test impact of restricting intraoperative benzodiazepines by randomly altering standard policy
  - pragmatic question about routine practice

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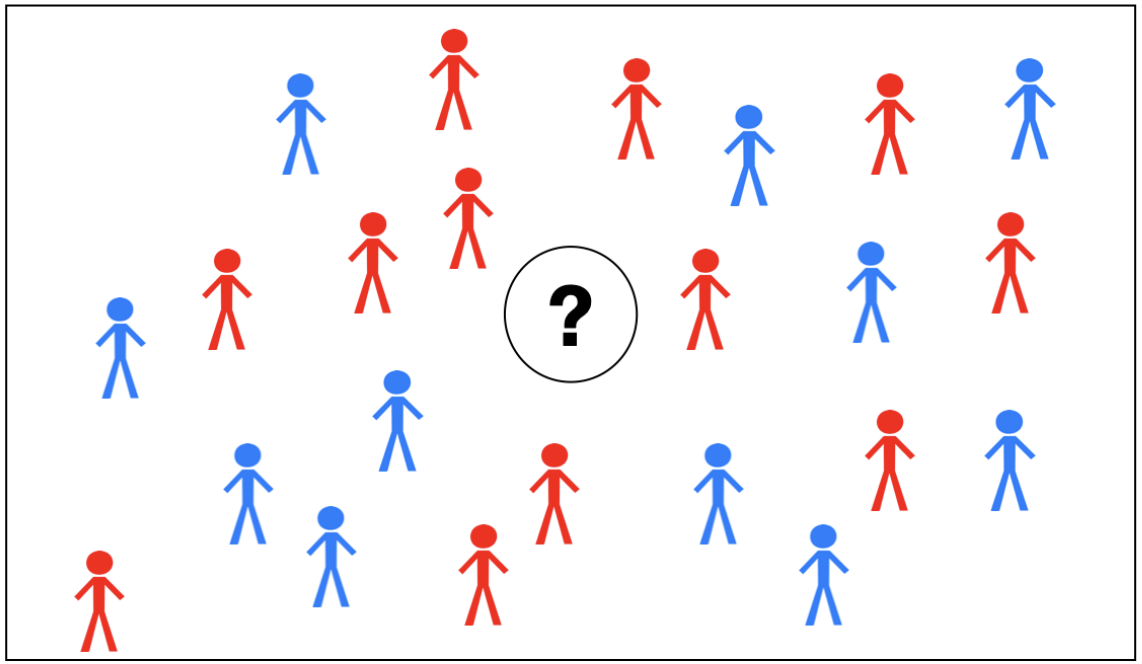
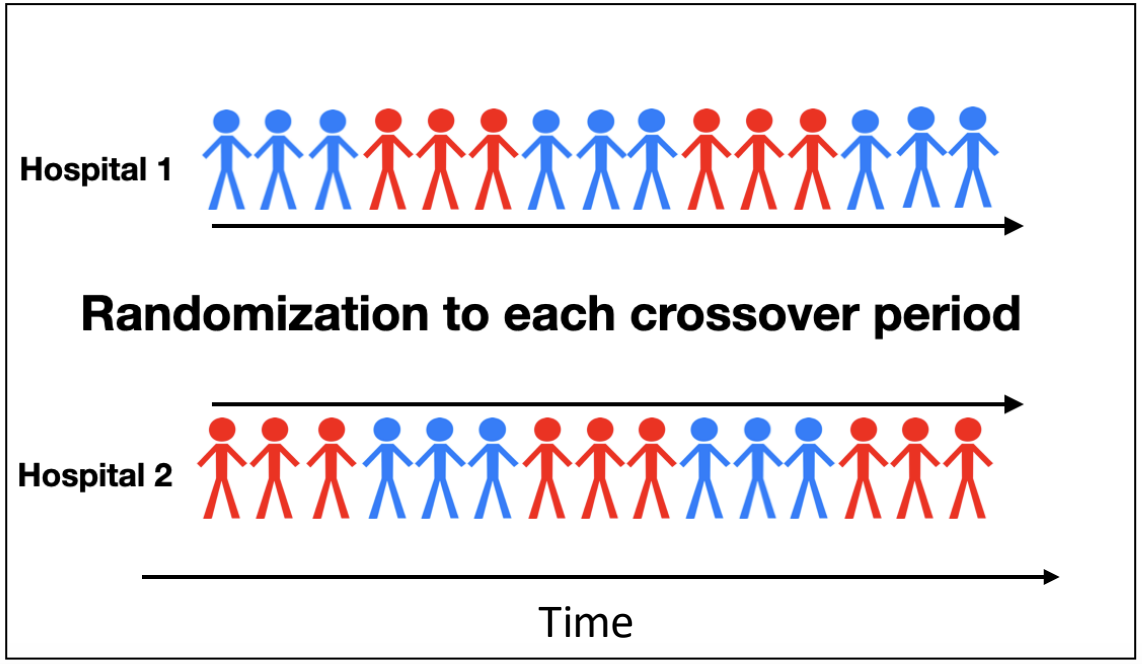
Current Practice

Haphazard



Cluster Crossover Trial

Random, Structured



Liberal

Restrictive

Study intervention arms

Restricted benzodiazepine policy	Liberal benzodiazepine policy
No routine administration of benzodiazepines	≥0.03 mg/kg Midazolam equivalent

Randomization schedule

- Policies applied during 12 to 18, 4-week crossover periods
- Sites randomized to all periods; 2 period blocks
  - 9 sites completed 18 periods
  - 2 sites completed 17 periods
  - 9 sites completed 12 periods

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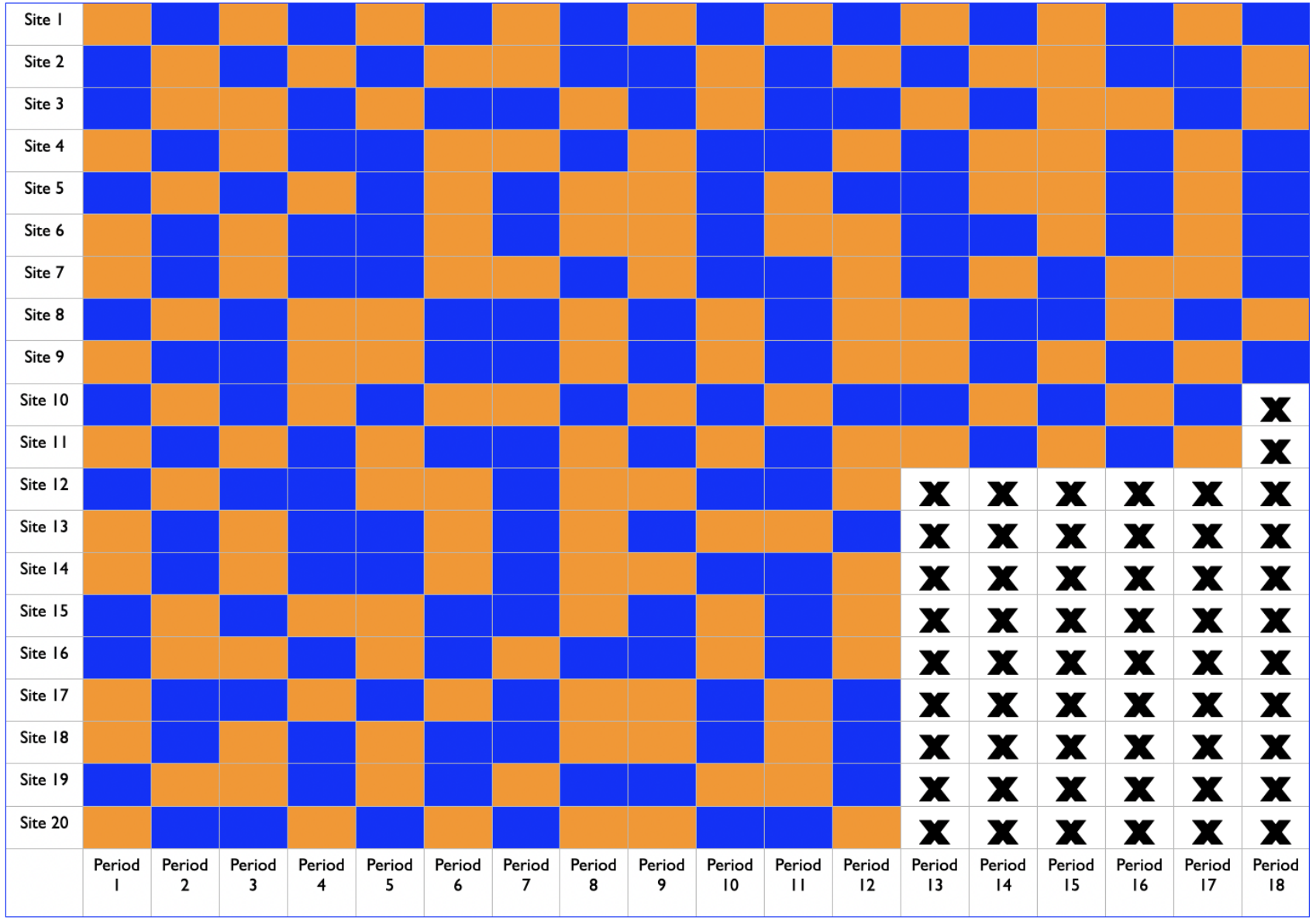
Randomization schedule

= Liberal

= Restrictive



Outcomes

- Primary outcome: delirium up to 72h after CV surgery
  - assessed by nurses in routine care
- Safety outcome: intraoperative awareness
- Post hoc outcome:
  - number of positive delirium assessments
- Secondary outcomes:
  - ICU and hospital LOS, in-hospital mortality

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Analysis

- Primary outcome: logistic mixed model

- All models:
  - fixed effects term for period
  - random effects to account for within-period ICC
  - adjusted for age, sex, emergency surgery, hx ETOH, and hx of home BZD use
  - Primary analysis: ITT

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Results

- 20 hospitals in Canada and US
- 19,768 patients
  - 9,827 restricted policy; 9,941 liberal policy
- Adherence to policy: **92.0%**
  - **91% restrictive, 93% liberal**

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Baseline characteristics

- Mean (SD) age: 65 (12) years
- Female patients: 27%
- Hx of home benzodiazepine use: 7%
- Hx of heavy ETOH: 5%

Surgical characteristics

- Surgical procedures
  - isolated CABG: 49%
  - isolated valve: 17%
  - other: 34%
- Emergency surgery: 8%
- Mean (SD) CPB time 116 (58) mins

Perioperative benzodiazepines

- Preoperative (within 24h): 16%
- Intraoperative
  - Restricted periods: 9%
  - Liberal periods: 93%
  - Mean (SD) dose when given (overall): 4.1 (2.5) mg
- Postoperative: 11%

Primary analysis population

Outcome	Restricted benzodiazepine policy (N=9827)	Liberal benzodiazepine policy (N=9941)	Adjusted OR (95% CI)	*P* value
Delirium up to 72h after cardiac surgery – no. (%)	1373 (14·0)	1485 (14·9)	**0·92** (0·84 - 1·01)	0·07

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Intraoperative awareness and # positive delirium assessments

Outcome	Restricted benzodiazepine policy (N=9827)	Liberal benzodiazepine policy (N=9941)	Adjusted RR (95% CI)	*P* value
Intraoperative awareness – no. (%)	0	0	n/a	n/a
Delirium assessments positive for delirium per 72 hours – crude mean (± SD)	0·3 (1·0)	0·4 (2·2)	**0·87 (0·78, 0·98)**	0·02

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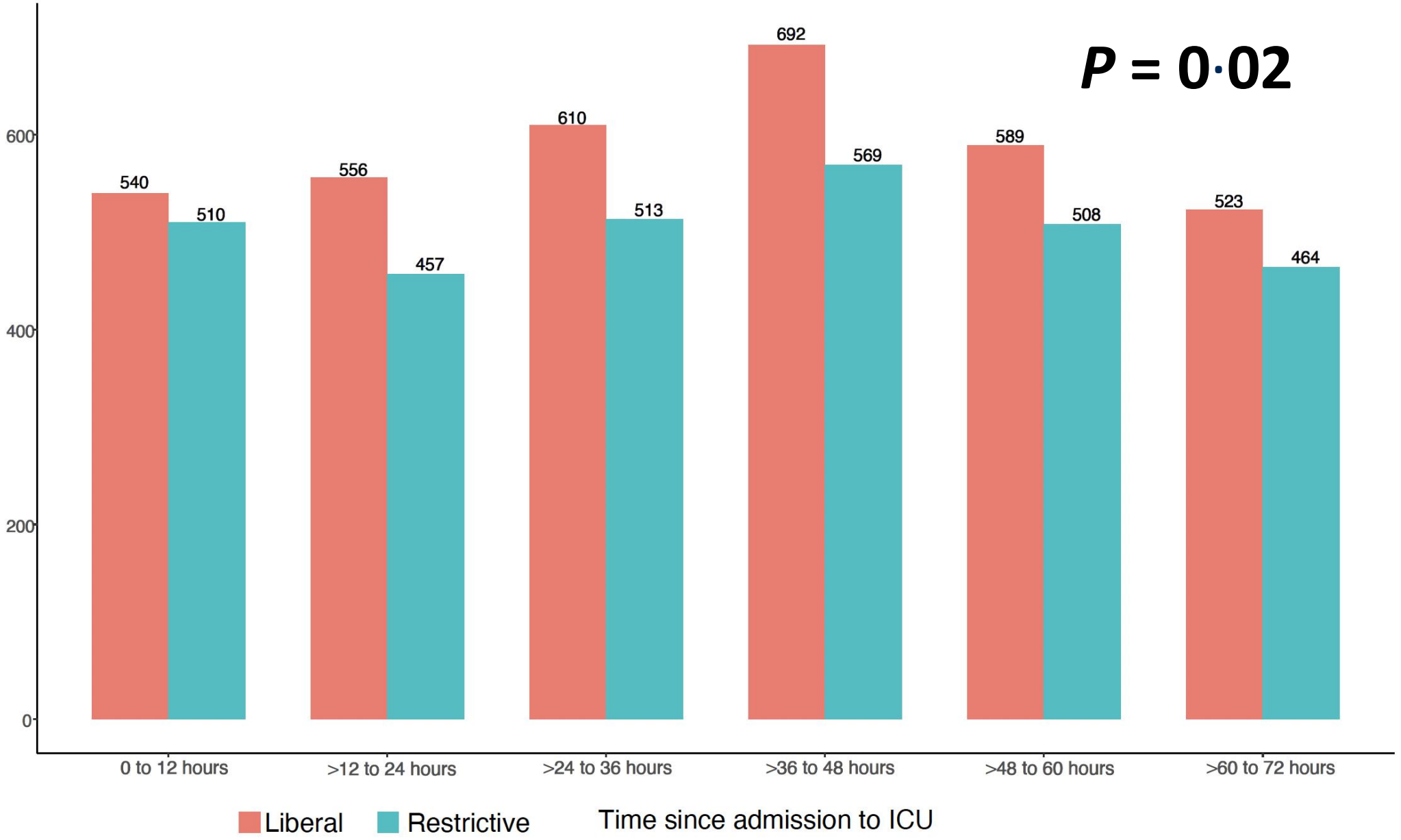
Number of positive delirium assessments



Secondary outcomes

Outcome	Restricted benzodiazepine policy (N=9827)	Liberal benzodiazepine policy (N=9941)	Summary estimate (95% CI)	*P* value
ICU LOS – LSM (95% CI)	3.5 (2.8, 4.5)	3.5 (2.7, 4.5)	**Mean difference** **0.04** (-0.12 - 0.27)	0.68
Hospital LOS – LSM (95% CI)	12.6 (11.5, 14.0)	12.7 (11.5, 14.1)	**Mean difference** **-0.05** (-0.53 – 0.31)	0.81
In-hospital mortality – no. (%)	298 (3.0)	272 (2.7)	**aOR 1.13** (0.95 - 1.34)	0.16

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Excluding restrictive arm patients who received BZD within 24h before surgery

Outcome	Restricted benzodiazepine policy (N=8391)	Liberal benzodiazepine policy (N=9941)	Adjusted OR (95% CI)	*P* value
Delirium up to 72h after cardiac surgery – no. (%)	1149 (13·7)	1485 (14·9)	**0·88** (0·81 - 0·97)	**0·01**

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Patients managed according to intraoperative policy

Outcome	Restricted benzodiazepine policy (N=9827)	Liberal benzodiazepine policy (N=9941)	Adjusted OR (95% CI)	*P* value
Delirium up to 72h after cardiac surgery – no. (%)	1219 (13·7)	1372 (14·8)	**0·90** (0·82 - 0·99)	**0·02**
Removing patients who received BZD within 24h from restrictive arm				
Delirium up to 72h after cardiac surgery – no. (%)	1024 (13·4)	1372 (14·8)	**0·87** (0·79 - 0·96)	**0·005**

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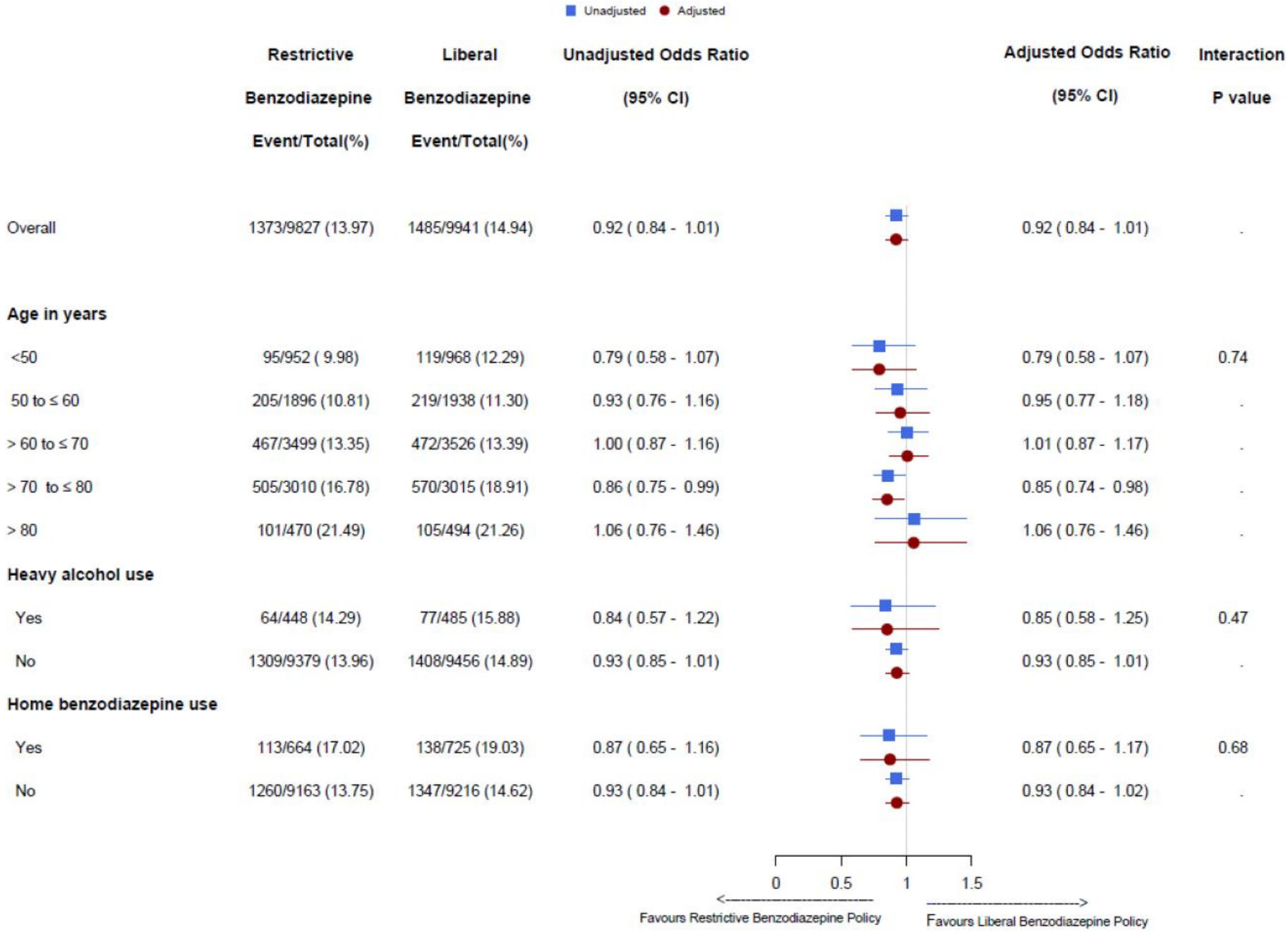
Unadjusted
Adjusted
Restrictive Benzodiazepine Event/Total(%)
Liberal Benzodiazepine Event/Total(%)
Unadjusted Odds Ratio (95% CI)
Adjusted Odds Ratio (95% CI)
Interaction P value
Overall 1373/9827 (13.97) 1485/9941 (14.94) 0.92 (0.84 - 1.01) 0.92 (0.84 - 1.01) .
Age in years
<50 95/952 (9.98) 119/968 (12.29) 0.79 (0.58 - 1.07) 0.79 (0.58 - 1.07) 0.74
50 to ≤ 60 205/1896 (10.81) 219/1938 (11.30) 0.93 (0.76 - 1.16) 0.95 (0.77 - 1.18) .
> 60 to ≤ 70 467/3499 (13.35) 472/3526 (13.39) 1.00 (0.87 - 1.16) 1.01 (0.87 - 1.17) .
> 70 to ≤ 80 505/3010 (16.78) 570/3015 (18.91) 0.86 (0.75 - 0.99) 0.85 (0.74 - 0.98) .
> 80 101/470 (21.49) 105/494 (21.26) 1.06 (0.76 - 1.46) 1.06 (0.76 - 1.46) .
Heavy alcohol use
Yes 64/448 (14.29) 77/485 (15.88) 0.84 (0.57 - 1.22) 0.85 (0.58 - 1.25) 0.47
No 1309/9379 (13.96) 1408/9456 (14.89) 0.93 (0.85 - 1.01) 0.93 (0.85 - 1.01) .
Home benzodiazepine use
Yes 113/664 (17.02) 138/725 (19.03) 0.87 (0.65 - 1.16) 0.87 (0.65 - 1.17) 0.68
No 1260/9163 (13.75) 1347/9216 (14.62) 0.93 (0.84 - 1.01) 0.93 (0.84 - 1.02) .
0
0.5
1
1.5
Favours Restrictive Benzodiazepine Policy
Favours Liberal Benzodiazepine Policy

Conclusions

- By ITT, restricted BZD policy did not reduce postoperative delirium
- No evidence of adverse events
  - no cases of intraoperative awareness reported
- On-policy analysis: ~10% reduction in delirium with BZD restriction
- Greater effect size the more that BZD exposure eliminated
- **Restricting benzodiazepines during cardiac surgery can be considered**

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Questions?

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